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A Phase I/II Investigation of Safety and Efficacy of Nivolumab and *nab*-Sirolimus in Patients With a Variety of Tumors With Genetic Mutations in the mTOR Pathway

ERLINDA M. GORDON, NICOLE L. ANGEL, NADEZHDA OMELCHENKO, VICTORIA S. CHUA-ALCALA, ANIA MORADKHANI, DORIS QUON and STEVEN WONG

Sarcoma Oncology Research Center, Santa Monica, CA, U.S.A.

Abstract. *Background/Aim: Advanced sarcoma has a poor prognosis. Dysregulation of the mammalian target of rapamycin (mTOR) occurs in various types of cancer. We aimed to determine the safety and efficacy of mTOR inhibitor nab-sirolimus when combined with the immune checkpoint inhibitor nivolumab. Patients and Methods: Previously treated patients ≥18 years with confirmed diagnosis of advanced sarcoma or tumor with mutations in the mTOR pathway were treated with 3 mg/kg nivolumab intravenously every 3 weeks; escalating doses of nab-sirolimus at 56, 75 or 100 mg/m^2 were administered intravenously on days 8 and 15 beginning in cycle 2. The primary aim was to determine the maximum-tolerated dose; we also determined disease control, objective response, progression-free survival, overall survival, and correlation between response using Immune-related Response Evaluation Criteria for Solid Tumors (irRECIST) versus RECIST v1.1. Results: The maximum-tolerated dose was 100 mg/m^2. There were two patients with partial response, 12 with stable disease and 11 with progressive disease. Median progression-free and overall survival were 12 and 47 weeks, respectively. The best responders (partial responses) were patients with undifferentiated pleomorphic sarcoma with loss of phosphatase and tensin homolog deleted on chromosome 10 (PTEN), tuberous sclerosis complex 2 (TSC2) mutation and estrogen receptor-positive leiomyosarcoma. Treatment-related adverse events of grade 3 or more included thrombocytopenia, oral mucositis, rash, hyperlipidemia and increased serum alanine aminotransferase. Conclusion: The data indicate that (i) treatment with nivolumab plus nab-sirolimus is safe with no unexpected adverse events; (ii) treatment outcome parameters were not improved by combining nivolumab with nab-sirolimus; and (iii) best responders were patients with undifferentiated pleomorphic sarcoma with PTEN loss and TSC2 mutation and estrogen receptor-positive leiomyosarcoma. Future direction in sarcoma research with nab-sirolimus will be biomarker-based (TSC1/2/mTOR, tumor mutational burden/mismatch repair deficiency etc.).*

Correspondence to: Erlinda M. Gordon, Sarcoma Oncology Research Center, Santa Monica, CA, U.S.A. Tel: + 1 3105529999, e-mail: egordon@sarcomaoncology.com

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Advanced solid malignancies are most often invariably fatal and innovative treatments are urgently needed. The mammalian or mechanistic target of rapamycin (mTOR) is a serine/threonine protein kinase forming the catalytic subunit of mTOR complex 1 (mTORC1) and mTORC2. These complexes are essential for the control of cellular growth, proliferation and survival (1). Specifically, mTORC1 plays a critical role in metabolism by suppressing catabolic pathways such as autophagy and increasing anabolism of proteins, lipids and nucleotides in response to changes in environmental conditions such as high stress or states of hypoxia (1). mTORC2 is primarily involved in cellular proliferation and survival by phosphorylating substrates that are involved in numerous aspects of cytoskeletal remodeling as well as cell migration (1). The most crucial role of mTORC2, however, is that it activates AKT serine/threonine kinase 1 (AKT), which is a major effector of insulin/phosphatidylinositol-4,5-*bis*phosphate 3-kinase (PI3K) signaling which then acts to inhibit several key substrates including the tuberous sclerosis complex 2 *(TSC2)*, which down-regulates mTORC1 (1). There are many growth factor pathways that converge at *TSC*. Mutations in *TSC1* or *TSC2* have been shown to cause hyperactivation of mTORC1 which normally down-regulates autophagy and up-regulates glucose metabolism, nucleotide synthesis and mRNA translation (2).

Rapamycin is an inhibitor of mTOR, which gives it immunosuppressive and anticancer properties (3). Numerous studies have shown that cancer cells significantly up-regulate

the PI3K/AKT/mTOR pathway, which makes this pathway an enticing target for anticancer therapies [reviewed in (4)]. *Nab*-sirolimus is a novel, albumin-bound rapamycin nanoparticle (formerly known as *nab*-rapamycin and ABI-009) designed to enhance drug delivery to target sites (5). *Nab*-sirolimus was recently approved as first-line treatment (6) of a rare subtype of soft-tissue sarcoma known as malignant perivascular epithelioid cell tumor (PEComa) (7). The aim of this phase I study was to determine the safety, maximum tolerated dose (MTD) and potential synergistic antitumor activities of nivolumab (8), an immune checkpoint inhibitor, combined with *nab*-sirolimus in a variety of advanced sarcomas and other tumors with genetic alterations sensitive to mTOR inhibitors.

Patients and Methods

Study design. This was an open-label, single-center, dose-finding phase IB study using a fixed dose of nivolumab and escalating doses of *nab*-sirolimus given intravenously. Patients were enrolled from September 2017 to July 2021. The study was conducted in accordance with the Declaration of Helsinki and approved by the Western Institutional Review Board (Protocol Code 20151429 on September 8, 2017) for studies involving humans.

The primary endpoint was determination of the MTD of *nab*-sirolimus when combined with nivolumab. Secondary endpoints included the disease control rate [DCR: complete response (CR) plus partial response (PR) plus stable disease] as determined by local radiological assessment using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 (9); the objective response rate (CR plus PR), and progression-free (PFS), and overall (OS) survival. Secondary endpoints also included determination of the median PFS and median OS.

The exploratory endpoint evaluated the correlation between response based on immune-related response criteria (irRECIST) (10) and that based on RECIST v1.1 (9) using Pearson's coefficient of correlation (11).

Dose-escalation phase I part of the study. The study employed the standard "cohort of three" design (12), wherein three patients were treated at each dose level with expansion to six patients per cohort when dose-limiting toxicity (DLT) was observed in one out of the three initially enrolled patients at each dose level. If no DLT occurred after two doses, escalation to the next dose level was permitted. The MTD was defined as the highest safely tolerated dose at which no more than one patient experienced DLT, with the next higher dose level having at least two patients who experienced DLT. Patients in the dose-escalation study were able to continue treatment at their designated dose levels for up to 18 3-week cycles or until significant disease progression or unacceptable toxicity occurred. No intra-patient dose escalation took place.

The dose of nivolumab given was 3 mg/kg intravenously over 30 min *q* 3 weeks (day 1 of every 21-day cycle) beginning in cycle 1. *Nab*-sirolimus was administered on days 8 and 15 beginning in cycle 2. Nivolumab was given first based on preclinical findings of increased efficacy when administered before *nab*-sirolimus (13). Escalating doses of *nab*-sirolimus were given intravenously over 30 min for 2 out of every 3 weeks starting from 56 mg/m^2 (n=3-6); 75 mg/m^2 (n=3-6) and 100 mg/m^2 (n=3-6).

Note that DLT included colitis, hepatitis, or pneumonitis of grade 3 or more; any grade 1-2 colitis, hepatitis or pneumonitis that recurred, worsened or persisted with oral steroids longer than 14 days; symptoms of adrenal crisis; any grade 4 hematological toxicity; or any non-hematological toxicity of grade 3 or more, according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) v4.03 (14). When DLT developed in more than one patient at 56 mg/m^2, the dose of *nab*-sirolimus was de-escalated to 45 mg/m^2 and to 30 mg/m^2 when a DLT developed at 45 mg/m^2.

Expansion phase II part of study. Following dose escalation, an additional 22-28 patients were to receive defined doses of nivolumab and *nab*-sirolimus at the MTD to assess overall safety and potential efficacy in a greater number of patients. Patients in the expansion phase of the study were able to continue treatment for up to 18 3-week treatment cycles or until significant disease progression or unacceptable toxicity occurred. The study was conducted in compliance with the International Conference on Harmonisation Good Clinical Practices (15).

After three or more treatment cycles, the principal investigator was able to recommend surgical debulking, complete surgical removal or a biopsy. If residual disease was present either by histopathological examination or by computerized tomography (CT) scan/magnetic resonance imaging (MRI), repeat treatment cycles could be given 2-4 weeks after surgery, when the surgical incision had healed, and if the patient had less than grade 1 toxicity.

Treatment was continued in the presence of increased tumor size by CT scan or MRI, indicating progressive disease by RECIST v1.1 (9) when there were no signs or symptoms indicating unequivocal progression, no worsening of Eastern Cooperative Oncology Group (ECOG) score attributable to progressive disease, no tumor growth at critical sites that was life-threatening, when the patient had signed an informed consent form that they were aware of alternative therapies but wished to defer these therapies, or when there was clinical benefit, as determined by the investigator.

Study population. Regarding sample size, 40-50 patients were to be enrolled. Patients who failed to become evaluable for the secondary endpoint with a follow-up CT/MRI were replaced. Tumors with histology of Ewing sarcoma, PEComa, epithelioid sarcoma, desmoid tumor, chordoma, non-small-cell lung cancer, small-cell lung cancer, urothelial carcinoma, melanoma, renal cell carcinoma, squamous cell carcinoma of head and neck, hepatocellular carcinoma, classical Hodgkin's lymphoma, microsatellite instability/mismatch repair deficiency (MSI-H/dMMR) metastatic colorectal cancer, and tumors with genetic mutations sensitive to mTOR inhibitors, were confirmed locally by the institution prior to enrollment.

Patient eligibility.

Inclusion criteria. A patient was eligible for inclusion in this study only when all of the following criteria were met:

- Histologically confirmed diagnosis of Ewing sarcoma, PEComa, epithelioid sarcoma, desmoid tumor, chordoma, non-small cell lung cancer, small cell lung cancer, urothelial carcinoma, melanoma, renal cell carcinoma, squamous cell carcinoma of head and neck, hepatocellular carcinoma, classical Hodgkin's lymphoma, MSI-H/dMMR metastatic colorectal cancer, and tumors with genetic mutations sensitive to mTOR inhibitors that were either metastatic or locally advanced and for which surgery was not a recommended option;

- One or more measurable target lesions by CT scan or MRI, measurable disease by RECIST v1.1, confirmed by investigator;
- Previous treatment completed after 5 half-lives or ≥28 days prior to enrollment, whichever was shorter;
- ≥40 kg For those aged 12-17 years, or 18 years or older, with Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1;
- Blood chemistry levels at screening (obtained ≤14 days prior to enrollment, local laboratory): Total bilirubin ≤1.5×upper limit of normal (ULN) mg/dl, aspartate aminotransferase/alanine aminotransferase ≤2.5×ULN (≤5×ULN if attributable to liver metastases), alkaline phosphatase <3×ULN (or ≥3×ULN when due to bone metastases), serum creatinine ≤1.5×ULN;
- Blood counts at screening (obtained ≤14 days prior to enrollment, local laboratory): Absolute neutrophil count ≥1.5×10^9/l, platelet count ≥100,000/mm^3 (100×10^9/l), hemoglobin ≥9 g/dl, serum triglyceride <300 mg/dl, serum cholesterol <350 mg/dl;
- Males and females of child-bearing age had to agree to use effective contraception 28 days before treatment with study drugs, while on study, and have a negative serum pregnancy test (human chorionic gonadotrophin) result at screening and to agree to have pregnancy testing during the study period, and after the end of treatment with study drugs. A second form of birth control was required even in the case of tubal ligation. Male patients were required to practice abstinence or agree to use a condom during sexual contact with a pregnant female or a female of childbearing potential while participating in the study. A second form of birth control was required even in the case of successful vasectomy;
- Life expectancy of ≥3 months, as determined by the investigator;
- Ability to understand and provide signed informed consent;
- Willingness and ability to comply with scheduled visits, laboratory tests, and other study procedures.

Exclusion criteria. A patient was not eligible for inclusion in this study when any of the following criteria applied:

- Known active uncontrolled or symptomatic central nervous system (CNS) metastases. For patients with controlled and asymptomatic CNS metastases, prior treatment for CNS metastases must have been completed ≥28 days (including radiotherapy/surgery) prior to the start of treatment in this study and should not be receiving chronic corticosteroid therapy for the CNS metastases;
- Active gastrointestinal bleeding;
- Uncontrolled pre-existing thyroid abnormality;
- Uncontrolled serious medical or psychiatric illness;
- 'Currently active' second malignancy, with the exception of patients with non-melanoma skin cancer, carcinoma *in situ* of the cervix, resected incidental prostate cancer (staged pT2 with Gleason Score ≤6 and postoperative prostate-specific antigen <0.5 ng/ml), or other adequately treated carcinoma *in-situ*; patients were not considered to have a currently active malignancy when they had completed therapy and were free of disease for ≥1 year;
- Liver-directed therapy within 2 months of enrollment. Prior treatment with radiotherapy [including radio-labeled spheres or CyberKnife, hepatic arterial embolization (with or without chemotherapy) or cryotherapy/ablation] was allowed when these therapies did not affect the areas of measurable disease being used for this protocol;
- Infection requiring systemic anti-infective treatment that was completed ≤14 days prior to enrollment (with the exception of uncomplicated urinary tract infection or upper respiratory tract infection);
- Uncontrolled diabetes mellitus as defined by HbA1c ≥8% despite adequate therapy;
- Unstable coronary artery disease or myocardial infarction during the preceding 6 months;
- Receipt of any concomitant antitumor therapy;
- History of interstitial lung disease, pneumonitis, or pulmonary hypertension;
- Use of strong inhibitors and inducers of cytochrome P450 3A4 (CYP3A4) in the 14 days prior to receiving the first dose of *nab*-sirolimus. Additionally, use of any known CYP3A4 substrate with narrow therapeutic window (such as fentanyl, alfentanil, astemizole, cisapride, dihydroergotamine, pimozide, quinidine, terfanide) within the 14 days prior to receiving the first dose of *nab*-sirolimus;
- Active hepatitis B or hepatitis C;
- Non-oncology vaccine therapy used for prevention of infectious disease within 4 weeks of trial enrollment;
- Autoimmune disease including rheumatoid arthritis, systemic progressive sclerosis (scleroderma), systemic lupus erythematosus, autoimmune vasculitis and motor neuropathy considered to be of autoimmune origin (*e.g.* Guillain–Barre syndrome);
- Systemic immunosuppression, including human immunodeficiency virus positive status with or without acquired immune deficiency syndrome;
- Skin rash (psoriasis, eczema) affecting ≥25% body surface area;
- Inflammatory bowel disease (Crohn's or ulcerative colitis);
- Ongoing or uncontrolled diarrhea within 4 weeks of trial enrollment;
- Recent history of acute diverticulitis, intraabdominal abscess or gastrointestinal obstruction within 6 months of trial enrollment (known risk factors for bowel perforation);
- Current, active or previous history of heavy alcohol abuse;
- Pituitary endocrinopathy;
- Adrenal insufficiency or excess.

Length of study. The study was expected to take approximately 32 months from the first patient enrolled to last patient follow-up, including approximately 24 months of enrollment, an estimated 6 months of treatment (or until treatment was no longer tolerated) and an end of treatment visit at 4 weeks (±7 days) after the last treatment.

The end of the study was defined as either the date of the last visit of the last patient, or the date of receipt of the last data point from the last patient that was required for primary, secondary, or exploratory analysis, as pre-specified in the protocol.

End of treatment for a patient was defined as the date of the last dose of nivolumab or *nab*-sirolimus. End of treatment visit for a patient was when safety assessments and procedures were performed after the last treatment, which had to be at least 4 weeks (±7 days) after the last dose of nivolumab or *nab*-sirolimus.

The follow-up period was the on-study time period after the end of treatment visit. All patients that discontinued the study drug and did not withdraw full consent to participate in the study continued in the follow-up phase for survival and initiation of anticancer therapy. Follow-up took place approximately every 12 weeks (±3 weeks), until death, withdrawal of consent, or study closure, whichever was the earliest. This evaluation may have been made by record review with/without telephone contact.

Statistical considerations.

Safety analyses: Demographic and baseline information (*e.g.*, extent of prior therapy) for study patients was tabulated. The number of

Table I. *Patients enrolled in the SOC-1701 study, according to race and sex.*

Sex	Race					
	White, not of Hispanic origin	Black, not of Hispanic origin	Hispanic	Asian or Pacific Islander	Unknown	Total
Male, n	10	1	6	2	0	19
Female, n	12	0	2	1	0	15
Total, n	22	1	8	3	0	34

Table II. *Patients enrolled in the SOC-1701 study, according to age group and sex.*

Sex	Age, years						
	18-28	29-39	45-50	51-61	62-72	73-83	Total
Male, n	7	6	3	0	1	2	19
Female, n	3	3	1	5	1	2	15
Total, n	10	9	4	5	2	4	34

patients studied for the dose-escalation part of the study was nine, and was 22 for the dose-expansion part.

For the phase I part of the study, the following information was reported for all adverse events observed: Dose level, type (organ affected or laboratory determination, such as absolute neutrophil count), severity [by CTCAE version 4.03 (14) and most extreme abnormal values for laboratory determinations] and relatedness to study treatment. For each dose, the number and percentage of patients experiencing any grade 3, 4, or 5 adverse event were reported, as well as the number and percentage of patients who experienced selected, specific types of adverse event. In addition, the DLTs were summarized by dose level and the MTD was determined.

For the phase I part of the study, the entire treated population (full analysis set) was that analyzed for all safety analyses. Summary tables included the number and percentage of patients with adverse events, serious adverse events, fatal adverse events and other adverse events of interest. Safety was analyzed in all patient groups together (metastatic and locally advanced disease). Frequency tables, graphs, and summary statistics were used for outcome data.

The incidence of all treatment-emergent adverse events were tabulated. Tables of fatal adverse events, serious adverse events, treatment-related adverse events, and adverse events leading to withdrawal from the study drugs were also collected.

For nivolumab and *nab*-sirolimus exposure, summary statistics were used for the total number of doses, average dose administered, and duration of each treatment.

Efficacy analyses: The disease control rate (CR, PR, SD), objective response rate (ORR), progression free survival (PFS) and overall survival (OS) were assessed by local radiological assessment using RECIST v1.1 (9) and irRECIST (10).

The focus of the study was to estimate the DCR in patients treated with nivolumab and *nab*-sirolimus. Patients who disease progressed before receiving *nab*-sirolimus were replaced and were not included in the statistical analysis. The number and percentage of patients achieving response was summarized.

Table III. *Histological cancer subtypes of patients enrolled in the SOC-1701 study.*

Histological cancer subtype	Patients, n
Osteosarcoma	10
Ewing sarcoma	5
Chondrosarcoma	4
Undifferentiated pleomorphic sarcoma	3
Desmoplastic small-cell tumor	2
Synovial sarcoma	1
Clear cell sarcoma	1
Chordoma	1
Serous carcinoma of endometrium	1
Myxoid liposarcoma	1
Colon cancer	2
Cervical adenosquamous cell carcinoma	1
Leiomyosarcoma	1
Pleomorphic Spindle cell sarcoma	1

Analysis of other efficacy endpoints, median PFS, and median OS were assessed for all tumor subtypes together.

The number of patients in each category was expected to be small; therefore, median PFS and median OS for these patients were summarized by descriptive statistics.

Exploratory analysis: Response based on RECIST v1.1 (9) was correlated with that based on irRECIST (10) using Pearson's coefficient of correlation (11).

Results

Demographic information. A total of 34 patients were included in this study. Table I shows the patients enrolled according to sex and race. There were 19 males and 15

females, of whom most (22/34) were White not of Hispanic origin. Table II shows the patients enrolled according to age group and sex. The majority (56%) were young adults between 18 and 39 years of age. Table III shows the histological tumor subtypes of patients enrolled in the study. Most patients (15/34) had osteosarcoma or Ewing sarcoma.

Summary of safety analysis. Thirty-one out of 34 patients who received at least one dose of *nab*-sirolimus were evaluable for the safety analysis.

In the phase I part of the study, no DLT occurred. The phase IB part of the study used the standard dose of 3 mg/kg nivolumab every 3 weeks and the MTD dose of 100 mg/m^2 *nab*-sirolimus on days 8 and 15 of each cycle.

AEs by body system. Table IV shows AEs by body system in the phase I part and expanded phase IB part of the study, toxicity grade, and attribution to treatment regimen. Twenty-five out of 31 (80.6%) patients who received at least one dose of *nab*-sirolimus had at least one treatment-related AE. The number of patients in the dose 3+ expanded phase IB category who had at least one treatment-related AE was 20 out of 25 (80%). Grade 3 adverse events that were considered to be related to nivolumab included increased thyroid-stimulating hormone (3.2%), while grade 3 AEs related to *nab*-sirolimus included thrombocytopenia (9.7%), oral mucositis (3.2%), increased thyroid-stimulating hormone (3.2%), acute dehydration (3.2%), hypertriglyceridemia (3.2%) and hypophosphatemia (3.2%).

Summary of efficacy analysis. Table V shows the best overall response, PFS and OS data of patients enrolled in the study. Thirty-one out of 34 patients who received at least one treatment cycle and had a follow-up CT scan were evaluable for best overall response, PFS and OS. Three patients did not receive *nab*-sirolimus.

The best responders (*i.e*. those with PR) were patients with undifferentiated pleomorphic sarcoma whose tumors had loss of phosphatase and tensin homolog, tuberous sclerosis complex 2 mutation, and leiomyosarcoma whose tumor was estrogen receptor-positive.

As of the data cut-off date, two patients (one with *TSC2* and another with *TP53* mutation) are still alive after 113 and 104 weeks, two patients with *EWSR*1–WT1 fusion are still alive after 104 and 106 weeks, and one patient with *PIK3CA* is still alive after 98 weeks.

Summary of exploratory endpoint analysis.

Correlation between RECISTv1.1 and irRECIST: We correlated response according to RECISTv1.1 and irRECIST using Pearson correlation. The Pearson correlation coefficient was 1.00 ($p<0.0001$), which represents perfect correlation.

Deaths: Table VI shows the list of deaths, Table VII shows the list of patients who withdrew due to an adverse event, and Table VIII shows patients who were lost to follow-up, therefore their survival status is not known. As of the data cut-off date, 23 patients have died from disease progression, eight with disease progression have been lost to follow-up and five patients are still alive. No patient died within 28 days of receiving *nab*-sirolimus.

Discussion

Immunotherapy has come of age and immune checkpoint inhibitors in the form of monoclonal antibodies that impede a cancer's ability to disable and elude the immune system have been approved by the US Food and Drug Administration at a rapid pace (16, 17). The goal of this phase I/II study was to determine if the combination of nivolumab and *nab*-sirolimus has synergistic activity and can improve the outcome of patients with advanced cancer in whose tumors dysregulation of the mTOR pathway has been determined. Nivolumab, an immune checkpoint inhibitor, is Food and Drug Administration-approved for various clinical indications (8). *Nab*-sirolimus gained FDA approval for locally advanced unresectable or metastatic malignant PEComa in 2021. In combination with nivolumab, the MTD of *nab*-sirolimus was 100 mg/m^2, which is the same as its MTD, the recommended phase II dose as a single-agent (7, 18).

A review of immune checkpoint inhibitors in advanced sarcoma showed three studies that demonstrated some activity of immunotherapy with or without chemotherapy in previously treated patients with advanced sarcoma. In 2017, the results were published of the SARC028 trial (NCT02301039) using pembrolizumab, a PD1-inhibitor, in 80 patients with previously treated advanced sarcoma (19), wherein seven (8%) patients with soft-tissue sarcoma, particularly undifferentiated pleomorphic sarcoma and dedifferentiated liposarcoma, had a partial response. Expansion of the SARC028 study showed 22.5% of patients with undifferentiated pleomorphic sarcoma had either CR or PR, and 10% of patients with liposarcoma had a PR (20). In 2018, the results of the ALLIANCE A091401 (NCT02500797) study were published, wherein patients with previously treated advanced sarcoma received either nivolumab alone or plus ipilimumab (an inhibitor of cytotoxic T-lymphocyte-associated protein). Only 5% in the nivolumab-treated cohort had a PR while 13.8% in the combination-treated cohort had a PR (21, 22). The median PFS was 2 and 4 months in the nivolumab and combination cohorts, respectively, which was not different from the results of chemotherapy (23). By indirect comparison, the results of combination nivolumab plus *nab*-sirolimus showed no difference in the outcome of patients compared

Table IV. *Adverse events related to study therapy, by grade*.

Adverse event		Grade of adverse event*					
		Related to nivolumab			Related to *nab*-sirolimus		
		1	2	3	1	2	3
Dose 1, 56 mg/m^2 *nab*-sirolimus, n=3							
Gastrointestinal disorders	Oral mucositis				2 (6.5%)		
General disorders	Fatigue	1 (3.2%)					
Investigations	Increased ALT		1 (3.2%)				
Metabolism and nutrition disorders	Hyperdyslipidemia						1 (3.2%)
Respiratory, thoracic and mediastinal disorders	Worsening hyperthyroidism		1 (3.2%)				
Skin and subcutaneous tissue disorders	Generalized skin rashes					1 (3.2%)	
Dose 2, 75 mg/m^2 *nab*-sirolimus, n=3							
Blood and lymphatic system disorders	Neutropenia				1 (3.2%)	1 (3.2%)	
Gastrointestinal disorders	Oral mucositis				2 (6.5%)		
General disorders	Intermittent fatigue				1 (3.2%)		
Investigations	Increased ALT			1 (3.2%)			1 (3.2%)
Respiratory, thoracic and mediastinal disorders	Pneumonitis	1 (3.2%)					
Skin and subcutaneous tissue disorders	Pruritic skin rashes				1 (3.2%)		
	Skin rashes					1 (3.2%)	
Dose 3, 100 mg/m^2 *nab*-sirolimus, n=3							
Blood and lymphatic system disorders	Neutropenia					1 (3.2%)	
Gastrointestinal disorders	Oral mucositis				1 (3.2%)		
Metabolism and nutrition disorders	Hypophosphatemia						1 (3.2%)
Skin and subcutaneous tissue disorders	Generalized Pruritis				2 (6.5%)		
	Pruritus left shoulder				1 (3.2%)		
	Skin rashes					1 (3.2%)	
	Skin rashes on face and chest wall				1 (3.2%)		
Expanded phase IB 100 mg/m^2 *nab*-sirolimus, n=22							
Blood and lymphatic system disorders	Neutropenia				1 (3.2%)		
	Thrombocytopenia				1 (3.2%)	4 (12.9%)	3 (9.7%)
Gastrointestinal disorders	Constipation, intermittent				1 (3.2%)		
	Diarrhea		3 (9.7%)		1 (3.2%)	2 (6.5%)	
	Hemorrhoid pain				1 (3.2%)	1 (3.2%)	
	Mouth sores				1 (3.2%)		
	Oral mucositis				4 (12.9%)	3 (9.7%)	1 (3.2%)
General disorders	Fatigue	2 (6.5%)			2 (6.5%)		
Infections and infestations	Herpes labialis	1 (3.1%)					
Investigations	Increased ALT		2 (6.5%)			2 (6.5%)	
	Increased AST		1 (3.2%)			1 (3.2%)	
	Weight loss of 9 kg					1 (3.2%)	
	Increased TSH level			1 (3.2%)			1 (3.2%)
Metabolism and nutrition disorders	Acute dehydration						1 (3.2%)
	Hypertriglyceridemia						1 (3.2%)
Musculoskeletal and connective tissue disorders	Arthralgia				1 (3.2%)		
	Increased back pain		1 (3.2%)				
	Right leg myalgia	1 (3.2%)					
Skin and subcutaneous tissue disorders	Alopecia				1 (3.2%)		
	Dry skin				1 (3.2%)		
	Facial acne					1 (3.2%)	
	General pruritus				1 (3.2%)	2 (6.5%)	
	Generalized skin rashes					1 (3.2%)	
	Increasing skin rashes, chest wall, pruritic					1 (3.2%)	
	Pruritic skin rashes on back				1 (3.2%)		

Table IV. *Continued*

Table IV. *Continued*

Adverse event		Grade of adverse event*					
		Related to nivolumab			Related to *nab*-sirolimus		
		1	2	3	1	2	3
	Pruritic skin rashes, bilateral upper extremities				1 (3.2%)		
	Pruritus of chest and upper extremities				1 (3.2%)		
	Scalp rashes				1 (3.2%)		
	Skin pruritus				1 (3.2%)		
	Skin rashes				6 (19.4%)	1 (3.2%)	
	Skin rashes bilateral upper extremities				1 (3.2%)		
Expanded phase IB + Dose 3, 100 mg/m^2 *nab*-sirolimus, n=25							
Blood and lymphatic system disorders	Neutropenia				1 (3.2%)	1 (3.2%)	
	Thrombocytopenia				1 (3.2%)	4 (12.9%)	3 (9.7%)
Gastrointestinal disorders	Constipation, intermittent				1 (3.2%)		
	Diarrhea		3 (9.7%)		1 (3.2%)	2 (6.5%)	
	Hemorrhoid pain				1 (3.2%)	1 (3.2%)	
	Mouth sores				1 (3.2%)		
	Oral mucositis				4 (12.9%)	3 (9.7%)	1 (3.2%)
General disorders and administration site conditions	Fatigue	2 (6.5%)			2 (6.5%)		
Infections and infestations	Herpes labialis	1 (3.2%)					
Investigations	Increased ALT		2 (6.5%)			2 (6.5%)	
	Increased AST		1 (3.2%)			1 (3.2%)	
	Weight loss of 9 kg					1 (3.2%)	
	Increased TSH level			1 (3.2%)			1 (3.2%)
Metabolism and nutrition disorders	Acute dehydration						1 (3.2%)
	Hypertriglyceridemia						1 (3.2%)
	Hypophosphatemia						1 (3.2%)
Musculoskeletal and connective tissue disorders	Arthralgia				1 (3.2%)		
	Increased back pain		1 (3.2%)				
	Right leg myalgia	1 (3.2%)					
Skin and subcutaneous tissue disorders	Alopecia				1 (3.2%)		
	Dry skin				1 (3.2%)		
	Facial acne					1 (3.2%)	
	General pruritus				3 (9.7%)	2 (6.5%)	
	Generalized skin rashes					1 (3.2%)	
	Increasing skin rashes, chest wall, pruritic				1 (3.2%)		
	Pruritic skin rashes on back				1 (3.2%)		
	Pruritic skin rashes, bilateral upper extremities				1 (3.2%)		
	Pruritus of chest and upper extremities				1 (3.2%)		
	Pruritus left shoulder				1 (3.2%)		
	Scalp rashes				1 (3.2%)	1 (3.2%)	
	Skin pruritus				1 (3.2%)		
	Skin rashes				6 (19.4%)	1 (3.2%)	
	Skin rashes bilateral upper extremities				1 (3.2%)		
	Skin rashes on face and chest wall				1 (3.2%)		

ALT: Alanine aminotransferase; AST: aspartate aminotransferase; TSH: thyroid-stimulating hormone. *There were no grade 4 adverse events.

Table V. *Efficacy analysis of best overall response, progression-free survival (PFS) and overall survival (OS) (n=31/34).*

		Best response, n		Median (range), weeks	
	Dose of *nab*-sirolimus	RECIST v1.1	irRECIST	PFS	OS
Phase I	Dose 1: 56 mg/m^2 (n=3)	SD: 1 PD: 2	SD: 1 PD: 2	6 (6-10)	22 (20-87)
	Dose 2: 75 mg/m^2 (n=3)	SD: 1 PD: 2	SD: 1 PD: 2	6 (6-16)	74 (31-110)
	Dose 3: 100 mg/m^2 (n=3)	SD: 3	SD: 3	34 (12-38)	66 (34-96)
Expanded phase IB	Dose 3+: 100 mg/m^2 (n=25)	PR: 2 SD: 12 PD: 11	PR: 2 SD: 12 PD: 11	12 (5-39)	47 (10-136)

(ir)RECIST: (Immune-related) Response Evaluation Criteria for Solid Tumors (9, 10); PD: Progressive disease; PR: progressive disease; SD: stable disease.

Table VI. *Deaths during the study.*

Case	Time from last dose to death, days
1	69
2	560
3	113
4	441
5	161
6	691
7	555
8	204
9	N/A
10	91
11	302
12	287
13	417
14	189
15	424
16	472
17	407
18	N/A
19	N/A
20	96
21	150
22	134
23	37

All deaths were due to disease progression, not attributable to a study drug.

Table VII. *Patients who withdrew from the study due to adverse event*

Case	Adverse event	Attributable to drug
1	Grade 2 pruritus	Yes
2	Grade 2 acneiform rash	Yes
3	Grade 2 mucositis	Yes
4	Thrombocytopenia	Yes
5	Grade 2 oral mucositis, grade 2 skin rash	Yes
6	Recurrent ascites	No

Table VIII. *List of patients who were lost to follow-up.*

Case	Time from last dose to last contact, days	Clinical status
1	0	Stable disease
2	36	Disease progression
3	124	Disease progression
4	710	Disease progression
5	228	Disease progression
6	7	Disease progression
7	140	Disease progression
8	134	Disease progression
9	21	Disease progression

with nivolumab alone (21, 22). Perhaps administering nivolumab with *nab*-sirolimus earlier in the course of the disease when cancer cells are most immunogenic (24) would have a better outcome as previously reported in the SAINT study using the combination of ipilimumab with nivolumab and trabectedin (25). Nevertheless, the study demonstrates the safety of this combination regimen with no additive toxicity. Treatment discontinuations were mainly due to disease progression. Although sirolimus was originally approved as an immunosuppressant (26, 27), there was no indication that *nab*-sirolimus hampered the efficacy of nivolumab immunotherapy in this study. Furthermore, this study provided insight into the potential efficacy of *nab*-sirolimus in patients with tumors having *TSC2* mutations. Given that mTOR pathway activation is often observed in solid tumors with *TSC1*- and *TSC2*-inactivating alterations, *TSC1*/*TSC2* would be a promising therapeutic target for *nab*-sirolimus. Biomarker analyses

from the AMPECT study and a *nab*-sirolimus expanded access program in patients with advanced malignant PEComa described antitumor activity in a subset of patients. In AMPECT, 89% of patients with pathogenic *TSC2*-inactivating alterations had a confirmed CR or PR. Likewise, objective responses and stable disease ≥12 weeks were observed in patients with pathogenic *TSC1*- or *TSC2*-inactivating alterations.

Conclusion

Taken together, these data indicate that: (i) The primary endpoint of the study was met. That is, *nab*-sirolimus given at its MTD/RP2D of 100 mg/m^2 may be combined with the immune checkpoint inhibitor, nivolumab, given at the standard dose of 3 mg/kg/dose; (ii) the combination nivolumab/*nab*-sirolimus did not improve treatment outcome parameters when compared historically with nivolumab alone; and (iii) PR in a patient with *TSC2*-mutated sarcoma parallels existing data that suggest TSC2 mutation is a target for *nab*-sirolimus. Thus, PRECISION 1, a phase II basket study using *nab*-sirolimus in patients with *TSC1* or *TSC2* mutation has been opened and is now enrolling patients (NCT05103358).

Conflicts of Interest

The Authors declare no conflicts of interest.

Author Contributions

Conceptualization: EMG, DQ and SGW; methodology: EMG and NLA; validation: EMG, DQ and SGW; formal analysis: EMG, VSC, DQ and SGW; investigation: EMG, VSC, DQ and SGW; data curation: EMG, DQ and SGW; writing – NLA, NO, EMG; writing – review and editing: NLA, NO, EMG, VSC, AM, DQ and SGW; supervision: EMG, DQ and SGW; project administration: VSC and AM; funding acquisition: EMG. All Authors have read and agreed to the published version of the article.

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References

1 Saxton RA and Sabatini DM: mTOR signaling in growth, metabolism, and disease. Cell *168(6)*: 960-976, 2017. PMID: 28283069. DOI: 10.1016/j.cell.2017.02.004

2 Reis LB, Filippi-Chiela EC, Ashton-Prolla P, Visioli F and Rosset C: The paradox of autophagy in Tuberous Sclerosis Complex. Genet Mol Biol *44(2)*: e20200014, 2021. PMID: 33821877. DOI: 10.1590/1678-4685-GMB-2020-0014

3 Seto B: Rapamycin and mTOR: a serendipitous discovery and implications for breast cancer. Clin Transl Med *1(1)*: 29, 2012. PMID: 23369283. DOI: 10.1186/2001-1326-1-29

4 Popova NV and Jücker M: The role of mTOR signaling as a therapeutic target in cancer. Int J Mol Sci *22(4)*: 1743, 2021. PMID: 33572326. DOI: 10.3390/ijms22041743

5 Desai N, Trieu V, Yao Z, Louie L, Ci S, Yang A, Tao C, De T, Beals B, Dykes D, Noker P, Yao R, Labao E, Hawkins M and Soon-Shiong P: Increased antitumor activity, intratumor paclitaxel concentrations, and endothelial cell transport of cremophor-free, albumin-bound paclitaxel, ABI-007, compared with cremophor-based paclitaxel. Clin Cancer Res *12(4)*: 1317-1324, 2006. PMID: 16489089. DOI: 10.1158/1078-0432.CCR-05-1634

6 Fyarro product information. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/213312lbl.pdf [Last accessed on March 14, 2023]

7 Wagner AJ, Ravi V, Riedel RF, Ganjoo K, Van Tine BA, Chugh R, Cranmer L, Gordon EM, Hornick JL, Du H, Grigorian B, Schmid AN, Hou S, Harris K, Kwiatkowski DJ, Desai NP and Dickson MA: *nab*-sirolimus for patients with malignant perivascular epithelioid cell tumors. J Clin Oncol *39(33)*: 3660-3670, 2021. PMID: 34637337. DOI: 10.1200/JCO.21.01728

8 Opdivo product information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/125554s070lbl.pdf [Last accessed on March 14, 2023]

9 Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, Rubinstein L, Shankar L, Dodd L, Kaplan R, Lacombe D and Verweij J: New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer *45(2)*: 228-247, 2009. PMID: 19097774. DOI: 10.1016/j.ejca.2008.10.026

10 Park HJ, Kim GH, Kim KW, Lee CW, Yoon S, Chae YK, Tirumani SH and Ramaiya NH: Comparison of RECIST 1.1 and iRECIST in patients treated with immune checkpoint inhibitors: a systematic review and meta-analysis. Cancers (Basel) *13(1)*: 120, 2021. PMID: 33561078. DOI: 10.3390/cancers13010120

11 Mukaka MM: Statistics corner: A guide to appropriate use of correlation coefficient in medical research. Malawi Med J *24(3)*: 69-71, 2012. PMID: 23638278.

12 Storer BE: Design and analysis of phase I clinical trials. Biometrics *45(3)*: 925-937, 1989. PMID: 2790129.

13 Hou S, Grigorian B, Schmid A and Desai N: Antitumor activity of ABI-009 (nab-rapamycin) in combination with anti-PD1 antibody in a syngeneic mouse model of B16 melanoma. Cancer Res *78(13)*: 3856-3856, 2018. DOI: 10.1158/1538-7445.AM2018-3856

14 National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.03. NIH Publication No. 09-5410. Bethesda, MD, USA, National Institutes of Health, pp. 1-78, 2010.

15 Dixon JR Jr: The International Conference on Harmonization Good Clinical Practice guideline. Qual Assur *6(2)*: 65-74, 1998. PMID: 10386329. DOI: 10.1080/105294199277860

16 Torralvo J, Friedlaender A, Achard V and Addeo A: The activity of immune checkpoint inhibition in KRAS mutated non-small cell lung cancer: a single centre experience. Cancer Genomics Proteomics *16(6)*: 577-582, 2019. PMID: 31659111. DOI: 10.21873/cgp.20160

17 Gordon EM, Angel NL, Kim TT, Brigham DA, Chawla SP and Hall FL: Immune and cell cycle checkpoint inhibitors for cancer

immunotherapy. Chapter 3. *In*: Advances in Precision Medicine Oncology. Arnouk H (ed.). Intech Open, 2021. DOI: 10.5772/intechopen.96664

18 Gonzalez-Angulo AM, Meric-Bernstam F, Chawla S, Falchook G, Hong D, Akcakanat A, Chen H, Naing A, Fu S, Wheler J, Moulder S, Helgason T, Li S, Elias I, Desai N and Kurzrock R: Weekly nab-Rapamycin in patients with advanced nonhematologic malignancies: final results of a phase I trial. Clin Cancer Res *19(19)*: 5474-5484, 2013. PMID: 24089446. DOI: 10.1158/1078-0432.CCR-12-3110

19 Tawbi HA, Burgess M, Bolejack V, Van Tine BA, Schuetze SM, Hu J, D'Angelo S, Attia S, Riedel RF, Priebat DA, Movva S, Davis LE, Okuno SH, Reed DR, Crowley J, Butterfield LH, Salazar R, Rodriguez-Canales J, Lazar AJ, Wistuba II, Baker LH, Maki RG, Reinke D and Patel S: Pembrolizumab in advanced soft-tissue sarcoma and bone sarcoma (SARC028): a multicentre, two-cohort, single-arm, open-label, phase 2 trial. Lancet Oncol *18(11)*: 1493-1501, 2017. PMID: 28988646. DOI: 10.1016/S1470-2045(17)30624-1

20 Burgess MA, Bolejack V, Schuetze S, Van Tine BA, Attia S, Riedel RF, Hu JS, Davis LE, Okuno SH, Priebat DA, Movva S, Reed DR, D'Angelo SP, Lazar AJ, Keung EZ-Y, Reinke DK, Baker LH, Maki RG, Patel S and Tawbi HA-H: Clinical activity of pembrolizumab (P) in undifferentiated pleomorphic sarcoma (ups) and dedifferentiated/pleomorphic liposarcoma (LPS): Final results of SARC028 expansion cohorts. J Clin Oncol *37(15_Suppl)*: 11015-11015, 2020. DOI: 10.1200/JCO.2019.37.15_suppl.11015

21 D'Angelo SP, Mahoney MR, Van Tine BA, Atkins J, Milhem MM, Jahagirdar BN, Antonescu CR, Horvath E, Tap WD, Schwartz GK and Streicher H: Nivolumab with or without ipilimumab treatment for metastatic sarcoma (Alliance A091401): two open-label, non-comparative, randomised, phase 2 trials. Lancet Oncol *19(3)*: 416-426, 2018. PMID: 29370992. DOI: 10.1016/S1470-2045(18)30006-8

22 Chen JL, Mahoney MR, George S, Antonescu CR, Liebner DA, Van Tine BA, Milhem MM, Tap WD, Streicher H, Schwartz GK and D'Angelo SP: A multicenter phase II study of nivolumab +/- ipilimumab for patients with metastatic sarcoma (ALLIANCE A091401): Results of expansion cohorts. J Clin Oncol *38(15_Suppl)*: 11511-11511, 2020. DOI: 10.1200/JCO.2020.38.15_suppl.11511

23 Demetri GD, Chawla SP, Ray-Coquard I, Le Cesne A, Staddon AP, Milhem MM, Penel N, Riedel RF, Bui-Nguyen B, Cranmer LD, Reichardt P, Bompas E, Alcindor T, Rushing D, Song Y, Lee RM, Ebbinghaus S, Eid JE, Loewy JW, Haluska FG, Dodion PF and Blay JY: Results of an international randomized phase III trial of the mammalian target of rapamycin inhibitor ridaforolimus versus placebo to control metastatic sarcomas in patients after benefit from prior chemotherapy. J Clin Oncol *31(19)*: 2485-2492, 2013. PMID: 23715582. DOI: 10.1200/JCO.2012.45.5766

24 Schreiber RD, Old LJ and Smyth MJ: Cancer immunoediting: Integrating immunity's roles in cancer suppression and promotion. Science *331(6024)*: 1565-1570, 2011. PMID: 21436444. DOI: 10.1126/science.1203486

25 Gordon EM, Chawla SP, Tellez WA, Younesi E, Thomas S, Chua-Alcala VS, Chomoyan H, Valencia C, Brigham DA, Moradkhani A, Quon D, Srikureja A, Wong SG, Tseng W and Federman N: SAINT: A phase I/expanded phase II study using safe amounts of ipilimumab, nivolumab and trabectedin as first-line treatment of advanced soft tissue sarcoma. Cancers (Basel) *15(3)*: 906, 2023. PMID: 36765863. DOI: 10.3390/cancers15030906

26 Dumont FJ and Su Q: Mechanism of action of the immunosuppressant rapamycin. Life Sci *58(5)*: 373-395, 1996. PMID: 8594303. DOI: 10.1016/0024-3205(95)02233-3

27 Sehgal SN: Sirolimus: its discovery, biological properties, and mechanism of action. Transplant Proc *35(3_Suppl)*: 7S-14S, 2003. PMID: 12742462. DOI: 10.1016/s0041-1345(03)00211-2

28 Dickson M, Ravi V, Riedel R, Ganjoo K, Van tine B, Chugh R, Cranmer L, Gordon E, Chen J, Murphy M, Schmid A, Desai N, Alonzo palma N, Kwiatkowski D and Wagner A: *nab*-Sirolimus for patients with advanced malignant PEComa with or without prior mTOR inhibitors: Biomarker results from AMPECT and an expanded access program. Journal of Clinical Oncology *40(16_Suppl)*: 11574-11574, 2022. DOI: 10.1200/JCO.2022.40.16_suppl.11574

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